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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/980,564 | 11/30/2001 | Andre Lieber | 30429-2USWO | 8863 |

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| EXAMINER | |
|---|---|
| MARVICH, MARIA | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1636 | |

DATE MAILED: 11/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/980,564 | LIEBER ET AL. | |
| | Examiner | Art Unit | |
| | Maria B Marvich, PhD | 1636 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *12 August 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *121-145* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *121-145* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

This office action is in response to an amendment filed 8/12/04. Claims 1-120 have been cancelled. Claims 121, 122, 129, 130 and 131 have been amended. Claims 121-145 are pending.

### *Response to Amendment*

Any rejection of record in the previous action not addressed in this office action is withdrawn. The new grounds of rejection herein were necessitated by amendment and, therefore, this action is final.

### *Specification*

The disclosure is objected to because of the following informalities: on page 86, line 15, B-gal is written as □–gal. Furthermore, the text on page 86 lines 10-20 references figure 17 but does not describe figure 17.

Appropriate correction is required.

### *Oath/Declaration*

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02. **This objection is maintained for reasons of record in the office action mailed 1/16/04 and is restated below.**

The oath or declaration is defective because:

Non-initialed and/or non-dated alterations have been made to the oath or declaration. Specifically, Denise Farrar has added #305 to the address. See 37 CFR 1.52(c).

***Response to Argument***

It is acknowledged that applicants have stated in the amendment filed 8/12/04that a new Oath/Declaration is being prepared and will be sent. Upon receipt of the new oath, the objection to the oath will be dropped.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 121-145 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. **This rejection is maintained for reasons of record in the office action mailed 1/16/04 and slightly amended based upon applicants' amendment.**

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat.

App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

**1) Nature of invention**. The instant invention is drawn to a recombinant double-stranded adenovirus vector comprising a parallel DNA strand and an anti-parallel DNA strand and three sets of inverted repeat sequences; 1) adenovirus ITR, 2) AAV ITR and 3) an unrecited source of IRs, and a heterologous promoter and a foreign gene sequence. The antiparallel strand of the recombinant adenovirus double-stranded DNA encodes a modified adenoviral fiber protein. The invention utilizes disciplines of molecular biology, cell biology and viral biology.

**2) Scope of the invention**. The adenoviral vector of the instant invention is designed to incorporate characteristics of several systems. The vector has altered or directed tropism for desired target cells by virtue of the modified fiber. Also the vector can integrate into a host cell chromosome based upon inclusion of the AAV ITR sequences. Finally, the inverted repeats appear to be used to generate a gutless vector by homologous recombination in which the surrounding adenoviral genome is recombined out of the vector. Each goal alone is complex and requires great skill in the art.

**3) Number of working examples and guidance**. The disclosure provides guidance for the generation of hybrid adenoviral vectors that have AAV ITR sequences and foreign genes under control of heterologous promoters inserted into an adenoviral vector. The disclosure provides further guidance for alteration or modification of the fiber proteins. The fiber proteins are truncated or deleted and replaced with fiber sequences (see page 83-86 which describes the generation of Ad5GFP/F35) from other serotypes or ligand peptide sequences are inserted into the fiber coding sequences (see page 95-98 which describes insertion of ligands into GH loops).

**4) State of Art**. The specification defines parallel and anti-parallel strands of DNA as referring to each of the strands of DNA of the double stranded adenovirus. Specifically, the anti-parallel strand of DNA is said to refer to the other of the two strands of DNA, which is not depicted in accompanying figures.

In contrast to the instant disclosure, the art does not teach that the double-strands of adenovirus DNA are referred to as parallel and antiparallel. Rather a review of the art has demonstrated that the strands of DNA are more commonly referred to as "r" and "l" strands and DNA in general is often referred to as comprising "sense" and "antisense" strands (see e.g. Hitt, Advances in Pharmacology page 139). Given the art and specification derived definitions, it appears that the parallel strand of the instant invention corresponds with the art defined "r" strand while the antiparallel strand corresponds to the "l" strand.

The specification also states that the fiber protein is encoded on the anti-parallel strand of DNA (page 19, line 24-30). Specifically, from the disclosure it appears that the fiber protein is produced by transcription in a 5' to 3' direction of what corresponds to the "l" strand. However, the art teaches that the fiber protein is encoded by the r-strand of the adenovirus genome or the top strand (see e.g. Hitt, Advances in Pharmacology page 139). Adding to the confusion the terminology depicting the location of the fiber protein, the specification describes fusion of the ad35 knob and shaft to the rail region of ad5 fiber coding sequences (page 85, which is illustrated in figure 18). The modified fiber protein in figure 18 shows that the coding sequences are from base 30,598 to base 32,781. Therefore, it appears here that the "parallel" strand encodes the fiber protein.

**5) Unpredictability of the art**. The development of adenoviral vectors for gene therapy is a complex art that requires great skill in the art furthermore, modification of the integrative ability **and** the tropism of the vector simultaneously requires a complex series of manipulations of the adenoviral genome. The instant recombinant double-stranded adenovirus vector comprising a parallel DNA strand and an anti-parallel DNA strand and three sets of ITR sequences from adenovirus, AAV and an unrecited source as well as an "antiparallel strand" that encodes a modified adenoviral fiber protein, which alters the tropism of the adenovirus vector, requires modifications of the adenoviral genome that are highly unpredictable given the lack of guidance in the instant specification.

Specifically, applicants recite that the fiber protein is encode by the "antiparallel" strand of the double stranded DNA. This configuration is not possible given the known genomic organization of adenovirus, which teaches that transcription of the adenovirus vector in a 5' to 3' direction on the upper strand produces the fiber protein mRNA. Therefore, the specification has not taught how the anti-parallel strand can be modified to express a modified fiber protein.

**6) Summary**. The invention recites a complex series of methods for the generation of a modified vector with altered tropism and that integrates into the host chromosome. The unpredictability of making the claimed invention is accentuated due to the lack of processes disclosed in the instant specification exacerbate a highly unpredictable art.

In view of predictability of the art to which the invention pertains and the lack of established clinical protocols and the inability to predict for whom the therapies would be required: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification.

Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have had to have conducted undue unpredictable experimentation in order to practice the claimed invention.

***Response to Argument- 112, first paragraph***

Applicants traverse the claim rejections under 35 U.S.C. 112, first paragraph on pages 22-28 of the amendment filed 8/12/04. Applicants argue that various heterologous peptides have been disclosed and that the disclosure teaches how to make a hybrid Ad.AAV vector comprising a nucleotide sequence encoding a modified fiber protein at Example II, Section G, at various sections between pages 83 and 85 and in figures 16A and 18.

Applicants' arguments filed 8/12/04 have been fully considered but they are not persuasive. Applicants have not addressed the basis of the enablement rejection. The rejection under 35 USC 112, first paragraph of claims 121-145 is based upon the recitation that the modified fiber protein is encoded by nucleotide sequences on the second or antiparallel strand. Applicants have defined parallel and antiparallel in the specification and indicate that the antiparallel strand encodes the fiber. However, the art does not recognize the fiber as being encoded by the antiparallel strand. While the parallel and anti-parallel strands both comprise the sequences that correspond to the fiber protein, as the strands are complementary, the fiber protein is correctly encoded by transcription of the parallel or "r" strand. To depict this more clearly, a diagram by Davison et al has been provided. The diagram depicts the gene arrangements for representative members of the adenovirus genera (see e.g. figure 2, Davison et al). In this figure, the fiber coding sequence is found on the "r" strand, which is confirmed by the text. On page 84,

col 2, Davison et al teach that the genomes of the adenovirus consist of a central block of rightward-oriented late gene from 52k to fiber and the opposing strand encodes the E2 gene. Chow and Broker teach that the fiber coding sequences generate r strand transcripts with tripartite leaders (see e.g. table 1). The fiber mRNA forms an unusual hybrid formation with l stand early transcripts that are comprised of convergent R loops with the adjacent L strand early message encoding the E19K and E11K proteins (see e.g. page 502, col 1, paragraph 2). The L strand early transcripts also give rise to rightward transcripts (see e.g. page 507, col 2, paragraph 2). Figure 2C illustrates the close relationship between fiber sequence and pVIII sequence, which is within 100 bases of the Y leader sequence of fiber. Taken together, this date demonstrates that it would be difficult to invert fiber-coding sequences to the antiparallel strand without upsetting the temporal and spatial arrangement of surrounding genes. Therefore, applicants have not demonstrated that the instant application is enabled for generation of a recombinant double-stranded adenovirus vector comprising a parallel DNA strand and an anti-parallel DNA strand and three sets of ITR sequences from adenovirus, AAV and an unrecited source as well as an "antiparallel strand" that encodes a modified adenoviral fiber protein, which alters the tropism of the adenovirus vector.

***Conclusion***

No claims are allowed.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (571)-272-0781. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Maria B Marvich, PhD
Examiner
Art Unit 1636

January 8, 2004

GERRY LEFFERS
PRIMARY EXAMINER